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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/352,466	07/13/1999	VIRGINIA C BROUDY	A-195CDD	2305
21069	7590	06/28/2006	EXAMINER	
AMGEN INC. MAIL STOP 28-2-C ONE AMGEN CENTER DRIVE THOUSAND OAKS, CA 91320-1799			BLANCHARD, DAVID J	
			ART UNIT	PAPER NUMBER
			1643	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/352,466

Applicant(s)

BROUDY ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 December 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 45-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 45-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Prosecution on the merits of this application is reopened on claims 45-70 in view of the Petition Decision mailed 3/16/2006.
2. Claims 1-44 are cancelled.

Claims 45-70 have been added.

Claims 45-70 are pending and under examination.
3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
4. This Office Action contains New Grounds of rejections.

Rejections Withdrawn

5. All rejections applied to claims 26-44 in the previous Office Action mailed 2/28/2005 are withdrawn in view of the cancellation of the claims.

New Grounds of Objections/Rejections

6. The disclosure is objected to because of the following informalities:
 - a. The specification at pg. 1, line 26 the terms "murine", "been" and "Cellular" are misspelled and require correction. Applicant's cooperation is requested in reviewing the entire disclosure for additional errors that require correction.
 - b. The Brief Description of the Drawings is objected to because Figure 6 contains parts A and B, however, the Description of the Drawings for Figure 6 refers to "Figure 7A" and "Figure 7B".

Appropriate correction is required.

7. Claims 45-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating leukemia cells comprising administering to an anti-neoplastic therapeutic agent conjugated to the monoclonal antibody produced from the hybridoma cell line ATCC No. HB 10716 (i.e., monoclonal antibody SR-1) or antigen-binding fragments thereof, wherein the monoclonal antibody or antigen-binding fragments thereof bind the human c-kit receptor and inhibit binding of human stem cell factor to the human c-kit receptor therapeutic, thereby decreasing the growth rate of human c-kit bearing cancer cells, does not reasonably provide enablement for a method of treating just any cancer comprising administering to a patient an anti-neoplastic therapeutic agent conjugated to just any monoclonal antibody or fragment thereof, wherein the monoclonal antibody or fragment thereof binds just any human stem cell factor receptor and inhibits binding of human stem cell factor to the human stem cell factor receptor, thereby decreasing the growth rate of human stem cell factor receptor bearing cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

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"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of treating cancer in a patient comprising administering to a patient an anti-neoplastic therapeutic agent conjugated to a monoclonal antibody or fragment thereof that binds to just any human stem cell factor receptor and inhibits binding of stem cell factor to the receptor, thereby decreasing the growth rate of the receptor-containing cells. Thus, the claims broadly encompass the treatment of just any cancer comprising administering just any monoclonal antibody conjugate that binds just any human stem cell factor receptor.

The specification teaches monoclonal antibody SR-1 produced by the hybridoma cell line ATCC No. HB 10716 that specifically binds the human c-kit receptor (see examples 2-4) and monoclonal antibody SR-1 blocks binding of radiolabelled human stem cell factor to the human erythroleukemia cell line, OCIM1, however, SR-1 does not block binding of radiolabelled art human stem cell factor to the murine MC/9 cell line (see example 5). The specification does not teach any other monoclonal antibody that binds the human c-kit receptor and inhibits binding of stem cell factor to the receptor or a monoclonal antibody that binds "a human stem cell factor receptor" that inhibits binding of stem cell factor to the receptor and neutralizes the biological effect of stem cell factor. There are no working examples of a monoclonal antibody other than monoclonal antibody SR-1 that binds the human c-kit receptor and blocks binding of

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stem cell factor or a monoclonal antibody that binds a human stem cell factor receptor and blocks binding of human stem cell factor to the receptor. There are now working examples of an *in vivo* cancer model system wherein administration of monoclonal antibody SR-1 inhibits binding of stem cell factor to the receptor and neutralizes the biological effect of stem cell factor, i.e., neutralizes the growth rate of cancerous cells in the subject. Therefore, the teachings in the specification are extremely narrow relative to the broad scope of the claims at issue. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that the "role of c-kit in cancer is somewhat ambiguous" pg. 69, 1st col. of Lennartsson et al, Current Cancer Drug Targets, 6:65-75, 2006. Lennartsson et al also teach that while a number of cancers are associated with the activation of c-kit, there are also a number of tumor forms, such as breast cancer, thyroid carcinomas and melanomas in which progression into a malignant phenotype occurs concomitantly with a loss of c-kit expression (pg. 69). According to applicants' specification, the prior art has not been able to obtain a monoclonal antibody to the c-kit receptor with any expectation that such a monoclonal antibody would possess the ability to block the binding of the c-kit ligand, stem cell factor (see specification at pg. 2). Further, the art of Ashman et al (J. Cell Physiol. 158:545-554, 1994) submitted by applicant as Exhibit A in the reply filed 12/29/05 teach three different monoclonal antibodies to the human c-kit receptor. Monoclonal antibody SR-1 potentially blocked the binding of stem cell factor to the human c-kit receptor on HEL-DR and MO7e cells,

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whereas monoclonal antibodies YB5.B8 and 17F11 had minimal effects on ligand binding. Further, SR-1 potently inhibited the proliferative response to stem cell factor, while 17F11 weakly inhibited and YB5.B8 had negligible effect. The specification teaches that monoclonal antibody SR-1 was produced by immunization of mice with cells of the OCIM1 line, however, immunization of mice with OCIM1 cells will not necessarily or predictably reproduce a monoclonal antibody possessing the properties of monoclonal antibody SR-1. There is insufficient guidance and direction to assist the skilled artisan in producing a monoclonal antibody other than monoclonal antibody SR-1 that binds the human c-kit receptor and inhibits binding of human stem cell factor to the receptor for the treatment of cancer. There is no direction or guidance provided by applicant to assist the skilled artisan in producing a monoclonal antibody that binds a human stem cell factor receptor and inhibits the binding of stem cell factor to the receptor. The skilled artisan could not predictably extrapolate the teachings in the specification, limited to the production of monoclonal antibody SR-1 specific for the human c-kit receptor to the production of just any monoclonal antibody that binds just any human stem cell factor that inhibits the binding of stem cell factor to the receptor for the treatment of just any cancer.

Further, as stated in the office action mailed 2/28/2005 one cannot extrapolate the teaching of the specification to the claims because Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39, cited on PTO-892 mailed 2/28/05) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a

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number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (bridging paragraph pp. 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Jain (Sci. Am 271:58, 1994, cited on PTO-892 mailed 2/28/05) discloses the art known barriers to the delivery of drugs into solid tumors. Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). The present disclosure provides no objective evidence or working examples for

treating cancer in a subject (i.e., *in vivo* animal model) to lend one of ordinary skill in the art a reasonable expectation of success. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with c-kit specific antibodies as discussed above.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Lennartsson et al, Ashman et al, Curi and Jain, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed method of treating any cancer in a patient comprising a monoclonal antibody conjugated to an anti-neoplastic agent wherein the monoclonal antibody binds just any human stem cell factor receptor and inhibits binding of human stem cell factor and decreases the growth rate of receptor containing cancer cells with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed cancer therapy and absent working examples providing evidence which is reasonably predictive that the claimed monoclonal antibodies bind a human stem cell factor receptor and inhibit the binding of stem cell factor to the receptor thereby decreasing the growth rate of just any cancer in a patient, commensurate in scope with the claimed invention.

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.


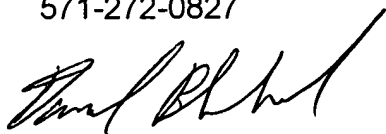
Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827



LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER